OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

Ottawa Hull K1A 0C9

(21) (A1) 2,188,143
(86) 1994/04/20
(43) 1995/11/02

(51) Int.Cl.[6] A61K 38/22

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Use of Brain Natriuretic Peptides (BNP), Phosphorylated Urodilatine, Phosphorylated CDD/ANP and Combinations Thereof

(72) Forssmann, Wolf-Georg - Germany (Federal Republic of) ;
Von Eickstedt, Klaus-Wolf - Germany (Federal Republic of) ;
Flüge, Thomas - Germany (Federal Republic of) ;

(71) HAEMOPEP PHARMA GmbH - Germany (Federal Republic of) ;

(57) 15 Claims

SMB

Use of Brain Natriuretic Peptide (BNP), Phosphorylated Urodilatin, Phosphorylated CDD/ANP and Combinations Thereof

The present invention pertains to the use of the peptide hormones brain natriuretic peptide (BNP), phosphorylated urodilatin, phosphorylated CDD/ANP, and combinations thereof for the treatment of pulmonary and/or bronchial diseases.

Obstructive respiratory tract diseases are characterized by a spasm of bronchial muscles, a swelling of bronchial mucosa, and an increased bronchial secretion in different intensities. They include, in particular, bronchial asthma, chronic-obstructive lung diseases (COLD), and cardinal asthma. A known therapy of obstructive respiratory tract diseases is administering β_2-sympathomimetics (e.g., fenoterol, salbutamol, terbutalen). β_2-Sympathomimetics decrease the tone of bronchial smooth muscles and, in addition, inhibit the release of mediators from mast cells and increase the mucociliary scavenging function. However, long-term and/or high-dosage application of β_2-sympathomimetics may result in a desensibilization of β_2-adrenoreceptors and thus in a strong decrease of therapeutic efficacy.

The bronchodilatory effect of urodilatin has been detected both in animal studies (Flüge, Hoymann et al., Naunyn-Schmiedebergs Arch. Pharmacol. 345 Suppl. 2, 24 (1992)) and in human asthma patients (Flüge, Wagner et al., Naun. Schmied. Arch. Pharmacol. 345 Suppl. 2, 23 (1992)).

Further, the bronchodilatory activity of atrial natriuretic peptide (ANP) in asthma has been known (Hulks et al., Br. Med. J. 299 (1989), 1081-1982).

It has been the object of the present invention to provide a new therapeutic agent for pulmonary and/or bronchial diseases, in particular obstructive respiratory tract diseases, which can be used instead of or in combination with known therapeutic agents, and has a superior degree of bronchodilatory activity to known agents, such as atrial natriuretic peptide and urodilatin.

The object according to the invention is achieved by providing a pharmaceutic composition containing brain natriuretic peptide (BNP), phosphorylated urodilatin, phosphorylated ANP or combinations thereof as the active ingredients, as well as optionally pharmaceutically usual diluents, vehicles, fillers or auxiliary agents, for the treatment of pulmonary and/or bronchial diseases.

The pharmaceutic composition is particularly useful for the treatment of obstructive respiratory tract diseases.

The composition is preferably administered parenterally, in particular intravenously (e.g. intravenous injections (as a bolus) or intravenous infusion), or by inhalation, the preferred dosage being from 5 ng to 1000 μg of brain natriuretic peptide (BNP) per kg of body weight, especially preferred from 10 ng to 100 μg of brain natriuretic peptide (BNP) per kg of body weight. Intramuscular, succutaneous or parenteral administrations with protective medication are also appropriate in the above-mentioned dosage.

In animal studies, it could be shown that parenteral administration of brain natriuretic peptide (BNP), phosphorylated urodilatin, phosphorylated ANP and combinations thereof in a bronchoconstriction caused by acetylcholin inhalation results in a distinct protection which is demonstrated, in particular, by an improved forced expiration.

Surprisingly, it has been established that the activities of brain natriuretic peptide (BNP), phosphorylated urodilatin, phosphorylated ANP and combinations thereof were clearly superior to

that of atrial natriuretic peptide (ANP) and urodilatin in the same dosage range.

The invention is further illustrated by the following example.

Example

The bronchodilatory effect of brain natriuretic peptide (BNP) was established in adult albino guinea pigs according to the method of Hutson et al. (Am. Rev. Respir. Dis. 137, 548; 1988) using the improved experimental design of Bent, Eltester, Forsting and Schmitz (Naunyn-Schmiedebergs Arch. Pharmacol. Suppl. 1, 381 (1992)). Awake animals were brought into a body box plethysmograph in which the extent of bronchoconstriction was measured by means of the respiratory pressure and the maximum of an inspiratory flow-volume curve. In addition, the respiratory rate and volume were measured. The animals were exposed to an aerosol of an 0.3% histamin solution in the breathing air for 30 seconds in order to achieve optimum brochoconstriction. Each animal served as its own control in preliminary experiments in which the extent of histamin challenge was established.

In the awake guinea pigs, brain natriuretic peptide (BNP) at an intraperitoneally injected dose of 320 ng of BNP/kg of body weight achieved a pronounced bronchodilatory effect which had a superior degree of activity to that of urodilatin at the same dosage. With 18 animals, atrial natriuretic peptide showed an even smaller bronchodilatory effect than urodilatin in these experiments. Thus, brain natriuretic peptide had a superior degree of activity to those of the peptides already described as having bronchodilatory activities.

C L A I M S :

1. Use of a pharmaceutic composition containing brain natriuretic peptide (BNP), phosphorylated urodilatin (P-Uro), phosphorylated ANP (P-CDD/ANP) or combinations thereof as the active ingredients, as well as optionally pharmaceutically usual diluents, vehicles, fillers or auxiliary agents, for the treatment of pulmonary and/or bronchial diseases.

2. The use according to claim 1 for the treatment of obstructive respiratory tract diseases.

3. The use according to claim 1 or 2, characterized in that said composition is administered parenterally, parenterally with protective medication, intramuscularly, subcutaneously, as an aerosol, by intravenous infusion or intravenous bolus administration, or by inhalation.

4. The use according to any of claims 1 to 3, characterized in that said composition containing any of the active ingredients mentioned in claim 1 or combinations thereof is administered in a dosage of from 5 ng to 1000 µg per kilogramm of body weight.

5. The use according to claim 4, characterized in that said composition containing any of the active ingredients mentioned in claim 1 or combinations thereof is administered in a dosage of from 10 ng to 100 µg per kilogramm of body weight.

6. Use of a pharmaceutic composition containing any of the active ingredients mentioned in claim 1 or combinations thereof and optionally pharmaceutically usual diluents, vehicles, fillers or auxiliary agents, for the preparation

of a medicament for the treatment of pulmonary and/or bronchial diseases.

7. The use according to claim 6 for the preparation of a medicament for the treatment of obstructive respiratory tract diseases.

8. The use according to claim 6 or 7, characterized in that a medicament is prepared which can be administered parenterally by intravenous route or by inhalation.

9. The use according to any of claims 6 to 8, characterized in that a unit dose of the medicament is administred which comprises from 5 ng to 1000 µg of an active ingredient as mentioned in claim 1 or any combination of such active ingredients per kilogramm of body weight.

10. The use according to claim 9, characterized in that a unit dose of the medicament is administred which comprises from 10 ng to 100 µg of an active ingredient as mentioned in claim 1 or any combination of such active ingredients per kilogramm of body weight.

11. A method for the treatment of pulmonary and/or bronchial diseases, characterized by administering a pharmaceutic composition containing any of the active ingredients mentioned in claim 1 or combinations thereof and optionally pharmaceutically usual diluents, vehicles, fillers or auxiliary agents.

12. The method according to claim 11 for the treatment of obstructive respiratory tract diseases.

13. The method according to claim 10 or 11, characterized in that said composition is administered parenterally by intravenous route or by inhalation.

14. The method according to any of claims 10 to 13, characterized in that said composition containing any of the active ingredients mentioned in claim 1 or combinations thereof is administered in a dosage of from 5 ng to 1000 µg per kilogramm of body weight.

15. The method according to any of claims 10 to 14, characterized in that said composition containing any of the active ingredients mentioned in claim 1 or combinations thereof is administered in a dosage of from 10 ng to 100 µg per kilogramm of body weight.

Abstract

Use of a pharmaceutic composition containing brain natriuretic peptide (BNP), phosphorylated urodilatin (P-Uro), phosphorylated ANP (P-CDD/ANP) or combinations thereof as well as optionally pharmaceutically usual diluents, vehicles, fillers or auxiliary agents, for the treatment of pulmonary and bronchial diseases.